Neurocognitive Degeneration

Introduction

Dementia is defined by a loss of cognitive function and memory impairment that exceeds those of normal cognitive aging. The reason for both dementia and normal cognitive aging is a loss of neurons. As humans age, neurons are lost. All patients will experience cognitive decline and impaired memory. That loss of neurons can be stifled—the more that synapses reinforce pathways, the more an individual engages their brain, the slower that loss will occur. A human can also engage in behaviors, such as heavy alcohol consumption, or experience disease, such as stroke or seizure, that lead to more abrupt cognitive decline. But in some genetically susceptible people, cognitive decline is accelerated by the accumulation of protein aggregates and the apoptotic loss of neurons—neurodegenerative disease.

Neurodegenerative diseases are characterized by the progressive loss of neurons and typically affect groups of neurons of a common tract, even if they are not immediately adjacent to each other. Each neurocognitive disease tends to have a predilection for a particular neural system and, therefore, has a stereotypical presentation that is fairly non-overlapping with others. However, all of them, if given enough time, will progress to widespread neuronal loss. The symptoms that each disease causes are based on where it starts.

Until recently, the diseases in this lesson were categorized as dementia disorders. All of them can lead to eventual cognitive decline as a result of neuronal loss. Medical science cataloged their signs and symptoms, determining which disease was present by its associated findings. The specific defects in cognition and changes in motor function enabled clinicians to make a clinical diagnosis and subsequently predict the MRI findings. Therefore, the syndromes were based on which cognitive or motor impairment was present and where atrophy was seen. We couldn't do anything about it, and we didn't know what was causing it.

What medical science has come to realize is that, although these diseases can be separated by their clinical manifestations and stereotypical findings on brain imaging, they are, in fact, NOT linked by dementia but by **infectious protein aggregates**. These protein aggregates accumulate in neurons, inducing their apoptosis. Neuronal death results in the spilling of these aggregates. This isn't just in the cell body, these protein aggregates can be found in axons; therefore, the entire tract is vulnerable to infection. Neighboring neurons take up these protein aggregates, accumulating ever more. This feeds the disease forward, with more aggregates made and more released as neurons subsequently die off.

Here's the thing: by the time symptoms are present, every neuron everywhere has some amount of protein aggregates. The ones that reach a critical concentration first, die off first. But the rest are very well along their way. You saw this in amyotrophic lateral sclerosis (ALS), in Motor and Sensory Tracts #3: *Spinal Cord Lesions*. And indeed, ALS is a neurodegenerative disease. Its symptoms are just so overtly motor-related that we included it there rather than here.

The protein that aggregates varies by disease. The syndromes are not defined by which aggregate accumulates, but rather **where** the aggregates accumulate **the most**, where the **neuron loss starts**. In every disease, if the patient survives long enough, the aggregates will claim all neurons.

We have chosen to teach a slight variation on what most textbooks would call neurodegenerative disorders. This lesson takes the clinical perspective (i.e., differential for dementia) with only a few select diseases with infectious protein aggregates chosen for discussion. For the sake of simplicity, we follow the time-honored classification based on the original descriptions of these diseases, focusing on these diseases, focusing on those that cause dementia and are thus named neurocognitive degeneration rather than neurodegeneration.

Prion disease isn't an important disease process in and of itself because it is so rare. However, it is the most severe, fastest-acting disease caused by protein aggregate accumulation and lays the foundation for comprehending the other neurodegenerative disorders.

There are multiple subtypes of prion disease, but they all come down to one protein—PrP. PrP^{c} is a cell-surface glycoprotein that is normally found in all neurons. When it undergoes a spontaneous conformational change to the evil **PrP^{Sc}** (Sc is for scrapie, the same disease process as seen in goats), it becomes **resistant to proteases**. PrP^{Sc}, independent of how it originates, then facilitates the conversion of other PrP^{c} proteins to PrP^{Sc}. It is this propagation of PrP^{Sc} that accounts for the transmissible nature of prion diseases.

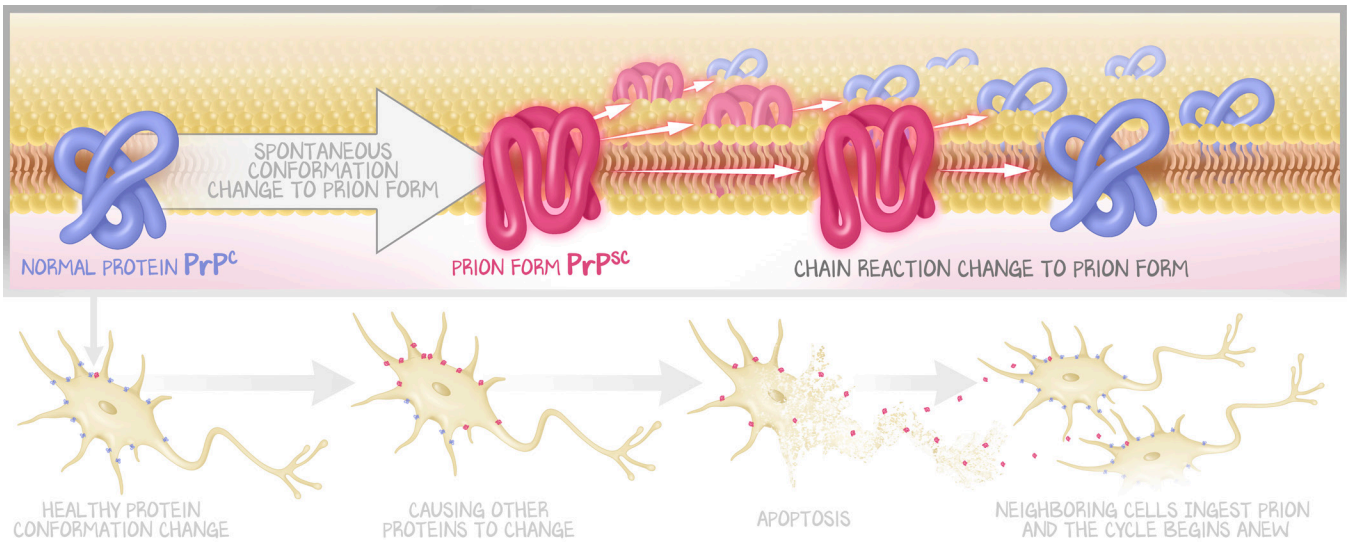

Figure 6.1: Mechanism of Prion Disease
When a normal protein (PrP^{C}) spontaneously converts to PrP^{Sc}, it not only instigates the conversion of more PrP^{C} to PrP^{Sc} in the affected neuron, but as the neuron undergoes apoptosis, it releases the PrP^{Sc}, which neighboring neurons uptake, repeating the process. Thus, neurons rapidly undergo apoptosis, resulting in the death of a patient within 6 months.

This capacity for a protein in an abnormal conformation to induce a similar structural change in other molecules as a self-propagating process has recently been demonstrated in each of the diseases discussed in this lesson. Prion disease is just **much faster** than the others that follow. From the time of symptom onset to death is less than 6 months. **Creutzfeldt-Jakob Disease** (CJD) is the most common prion disease, occurring in 1 per 1,000,000 people. You will never see a case of CJD. The most common ways of **acquiring** CJD were from transplanting neural tissue (corneal transplant), ingesting neural tissue (cannibalism caused Kuru), and sticking things into neural tissue (deep brain electrodes). We are more careful now, so the most likely mechanism will be a sporadic mutation in the *PRNP* gene. The incidence is highest in the seventh and eighth decades of life. There is a rapid decline in memory, behavior, and motor function, with severe cognitive defects, memory impairment, and spastic contractions of the extremities.

Vacuolization of neurons is seen universally in prion disease, but the mechanism by which it happens is unclear. The protein spreads rapidly and involves the cerebellum, striatum, and most of the cortex.

The importance of this disease is that it demonstrates the infectious protein process. Proteins accumulate and neurons die off, releasing the protein to neurons around them, even at synapses. The protein is taken up by other neurons, which suffer the same fate and accelerate the disease process by having more protein converted within them, leading to the accumulation of more and more protein aggregates.

DISEASE	PRIMARY DYSFUNCTION	PRIMARY LOCATION	INCLUSIONS
Alzheimer's disease (AD)	Dementia, memory	Hippocampus	Aβ (plaques, causative) τ (tangles, present)
Frontotemporal lobar degeneration (FTLD)	Behavioral changes, language disturbance Loss of inhibition	Frontal lobe Hippocampus	τ
			TDP-43
			FUS
Parkinson's disease (PD)	Bradykinetic movement	Substantia nigra	α-synuclein
Huntington's disease (HD)	Hyperkinetic movement disorder	Striatum	Huntingtin (polyglutamine)
Amyotrophic lateral sclerosis (ALS)	Weakness with upper and lower motor neurons signs	Motor neurons	

Table 6.1: Neurocognitive Degeneration

Alzheimer's

Alzheimer's disease is the most common cause of dementia in the United States. The clinical features are a loss of memory and impaired attention. Personality, motor, and sensation remain intact. The area of most atrophy or the first area to experience atrophy is the hippocampus of the temporal lobe. The pathogenesis is not completely understood at this time. We do know that there are two abnormal proteins—amyloid β (Aβ) and tau (τ). However, as we postulate in this section, τ is likely a symptom rather than a cause.

Aβ generation is the critical initiation event for the development of the neurodegenerative disorder with the phenotype of Alzheimer's disease. To support this claim, there are diseases in which τ deposits appear, such as frontotemporal lobar degeneration, progressive supranuclear palsy, and corticobasal degeneration, but neither Aβ deposits nor the symptoms of Alzheimer's disease develop. And there is good evidence based on familiar forms or causes of early-onset disease—ApoE (*APOE*), trisomy 21, and presenilin-1 (*PSEN1*).

In **Trisomy 21** (Down's syndrome), there is an extra copy of chromosome 21. A transmembrane protein found in neurons and glial cells alike, amyloid precursor protein (APP), is encoded by the *APP* gene. It is constitutively expressed by neurons and glial cells as it is a regular part of the plasma membrane. Therefore, having three copies of the gene will produce about 50% more APP than normal. Patients with trisomy 21 have cognitive impairments—intellectual disability—with varying degrees of severity. However, even those with only mild impairments experience cognitive decline and impaired memory as early as their 20s or 30s (normal onset is 60s and 70s). The accelerated onset of Alzheimer's disease isn't the same in all patients with trisomy 21; thus, it isn't causal, but APP production is strongly indicated to be a risk factor.

The causal link between apolipoprotein E (**ApoE**) and Alzheimer's isn't established, but it certainly plays a role. There are three possible *APOE* alleles—2, 3, and 4—based on two amino acid isoforms. The gene dosage of $ApoE_4$ is correlated to increased risk. Having one copy of *APOE4* is bad, having two copies is worse. Conversely, $ApoE_2$ is protective from Alzheimer's disease, likewise in a gene dosage-dependent fashion.

Aβ is a cleavage product of APP. Periodically, as part of normal plasma membrane remodeling, APP is recycled. Follow along with Figure 6.2, below. APP is recycled via both extracellular and intracellular cleavage. The final step is always carried out by γ-secretase, the intracellular cleavage protein. When things go well, the first cut is made by α-secretase. This removes an extracellular APPsα (a soluble extracellular protein) from APP, leaving behind **αAPP in the membrane**. When γ-secretase makes its cut, healthy, soluble p3 peptide is released into the extracellular environment. What happens intracellularly doesn't matter. But if **β-secretase** makes that first cut, a shorter APPsβ (also soluble, so not the problem protein) is released, leaving behind βAPP in the membrane. When γ-secretase cleaves βAPP, it releases **insoluble Aβ protein** instead of the usual soluble p3 into the extracellular space. Astrocytes and neurons can't process the Aβ proteins, so they accumulate. Then, they form **Aβ protein aggregates**, forming **Aβ plaques**. The neurons don't like plaques, and the astrocytes don't either. But neither are equipped to deal with the plaques. We're going to come back to what "don't like plaques" means.

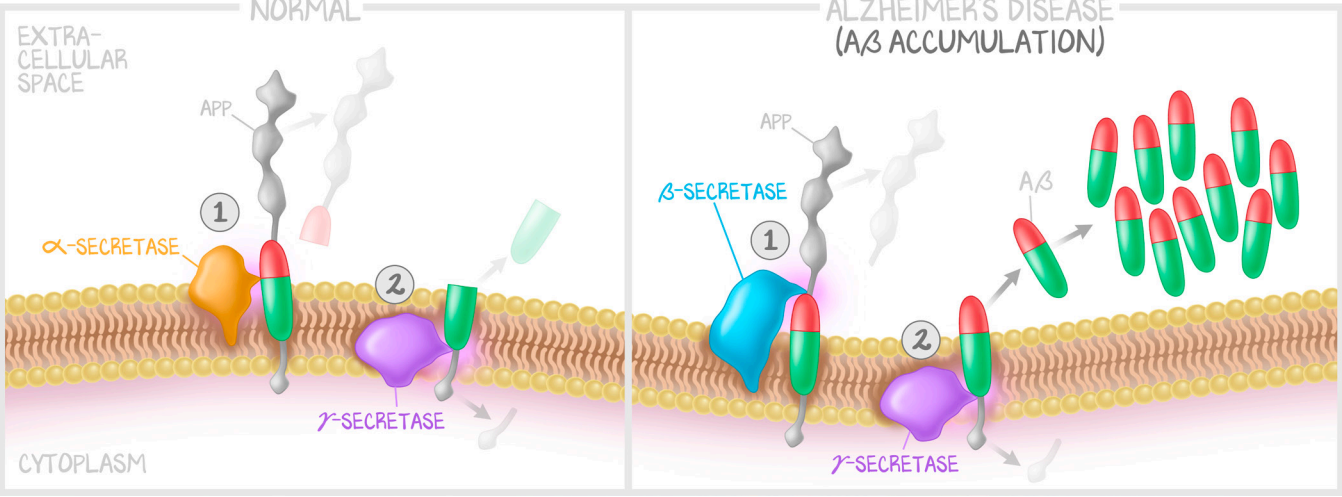

Figure 6.2: Aβ Pathogenesis
When the sequence is α-secretase then γ-secretase, the result is two soluble molecules. When the sequence is β-secretase then γ-secretase, the result is an insoluble Aβ protein that accumulates outside the affected neuron, forming the Aβ plaque.

τ is a microtubule-associated protein (MAP) that supports and maintains the axon microtubules. When **τ is** phosphorylated, it is more likely to dissociate from the microtubule it was bound to. **Neurofibrillary tangles** are a histological hallmark of Alzheimer's, but they are also found in other neurocognitive diseases. Neurofibrillary tangles are made of **hyperphosphorylated τ protein aggregates**. These neurofibrillary tangles are found in the axons and cell bodies that encounter an **Aβ plaque**. Aggregated τ is also present in dystrophic neurites that form the outer portions of neuritic plaques and axons coursing through the affected gray matter. **Wherever there are plaques outside** the cell, **tangles develop inside** the cell and only at that spot.

This next sentence is our inference, not something that has been proven. It really seems that certain neurons express more APP than other neurons, and those are the ones that make the plaques. The neuron that makes the plaque doesn't like the plaque, as evidenced by the changes in the plasma membrane of the neuron near the plaque, the same location that the τ tangles form in the cell body. Other neurons don't like the plaque, as evidenced by histology; wherever a plaque is, the part of another cell in contact with the plaque—be it axon, dendrite, cell body, whatever—will develop τ tangles. It seems like the plaques cause the neurons to freak out whenever they're touched by one. "Freaking out near a plaque" leads to something that medical science has not yet elucidated that changes the

phosphorylation of cytoplasmic molecules at that spot. τ is likely phosphorylated secondarily, a result of locally upregulated kinases. It just so happens that τ is really vulnerable to phosphorylation, and phosphorylation causes τ to release its microtubule. And because they are only hyperphosphorylated at that spot, more and more τ molecules try to pass through that spot only to be phosphorylated and dissociate. The dissociation of τ proteins over time results in the tangle.

The typical Alzheimer's patient is one with **progressive memory loss**. The neurons that are affected first and in greatest severity are in the **hippocampus**, the memory storage part of the brain. The patient first loses the ability to form new memories. Short-term memory and attention may be retained early in the disease. Then, short-term memory is lost altogether, followed by the subsequent loss of long-term memory (retrograde amnesia). The person will not recall recent events, some patients in no more than a 10-second loop, and will often become disoriented, not remembering their own house or spouse. With the degeneration of cortical mass, the remaining space is filled with CSF. There will be overall atrophy, most pronounced in the hippocampus.

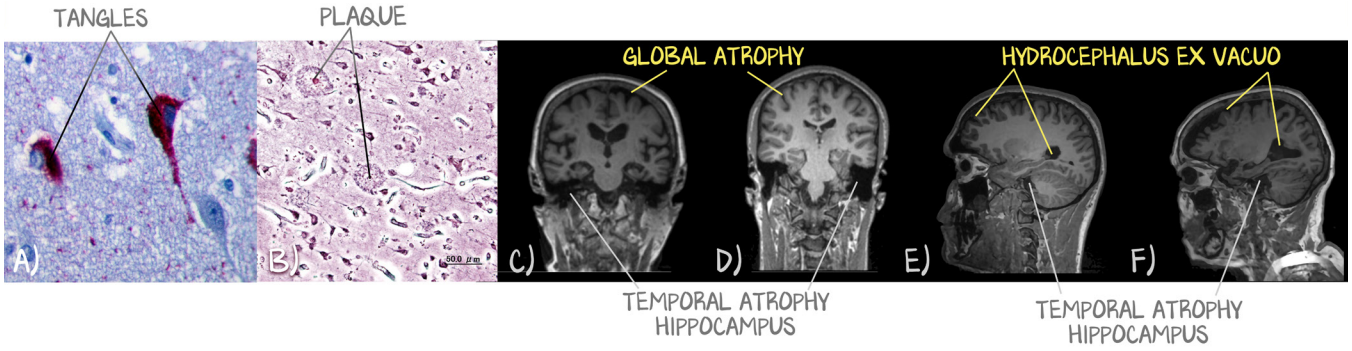

Figure 6.3: Alzheimer's Disease
(a) Neurofibrillary tangles of hyperphosphorylated τ protein. (b) Two plaques are visible, and only the top plaque demonstrates a neuron. At this magnification, neurites are not visible. (c) Coronal T1-weighted MRI from a patient with Alzheimer's disease for comparison with (d), a normal coronal section from approximately the same location. Notice the disproportionate temporal atrophy in addition to hydrocephalus and superior atrophy. Panels (e) and (f) show sagittal views from the same patients as in (c) and (d), respectively, demonstrating severe degeneration of the temporal lobe in the patient with Alzheimer's disease.

Although histologically, the disease burden (i.e., the severity of memory and cognitive impairment) is better correlated to the number of τ tangles than the number of Aβ plaques, Alzheimer's disease is not based on brain biopsy. And, consistent with our theory, more tangles indicates more severe disease burden, the two symptoms—τ tangles and impaired cognition—advancing together. Medical science possesses the ability to perform functional MRI, evaluate the current Aβ plaque burden, and reliably deduce when dementia will set in. This isn't helpful yet, as there are no Aβ plaque-removing medications. Future treatments could facilitate Aβ plaque removal or target β-secretase to prevent more Aβ from being released.

Nothing has been found to slow the disease progression. Acetylcholine and glutamate are excitatory neurotransmitters. There have been trials that demonstrate that **glutamate antagonists** (such as memantine) and **acetylcholinesterase inhibitors** (donepezil) improve quality of life. The benefit derived is empirical, so the mechanism need not be explored. Once symptomatic, the average lifespan is 5–10 years with a progressive decline in cognitive and, eventually, motor function. Death is often secondary to infection. Like the other neurodegenerative diseases, the medications improve symptoms but do not affect the progression of the disease.

Frontotemporal Lobar Degenerations (FTLDs)

FTLDs are a heterogeneous set of disorders (plural) that share a common phenotype—disinhibition, loss of social grace, personality changes, and memory loss. They affect the **frontal lobes** first and more severely than the **temporal lobes**. Given long enough, just as in any of the protein-aggregate diseases, all neurons will be claimed. The description of these disorders often confuses learners as they are also studying Alzheimer's. The opening sentence was written deliberately. FTLDs don't affect the frontal lobes and temporal lobes, just as Alzheimer's doesn't affect the frontal lobes and temporal lobes—that would being saying they are identical. Alzheimer's takes the temporal lobes first and foremost, and late in the disease, the frontal lobe is the next vulnerable area taken, followed by the disease spreading elsewhere. In a similar vein, **FTLDs take the frontal lobe first**, then late in the disease, **the temporal lobe is the next vulnerable area taken**, followed by the disease spreading to the rest of cortex.

Formerly known as frontopolar dementia and by its eponym "Pick's disease," FTLDs are yet another example of aggregate protein deposition causing neuronal apoptosis. The term FTLD is now preferred because it accurately depicts the lobes that are most affected, even listing them in the order that they are most affected. In all FTLDs, loss of the frontal lobe results in personality and behavior changes. Patients with FTLDs are **compulsive**, demonstrate a **loss of social restraint**, and sometimes **loss of empathy**. That is because the back of the frontal cortex is dedicated to movement, but the front of the frontal cortex is where personality, behavior, mood, and cognition interact with the subcortical tracts (down to the basal ganglia). The disease progresses posteriorly through the frontal lobe, and at end stage, there may be a loss of movement (premotor and motor cortex) or the inability to speak (Broca's area).

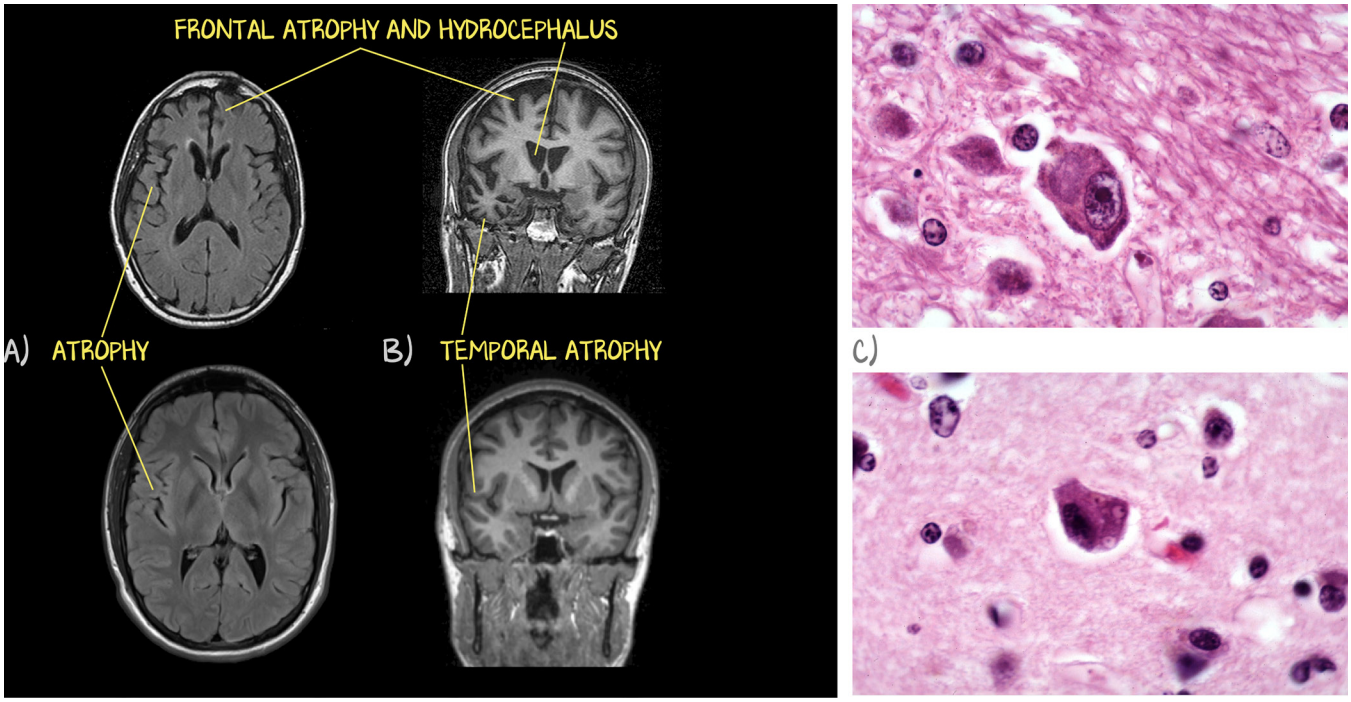

Figure 6.4: Frontotemporal Lobar Degeneration
(a) Comparison between a patient with FTLD (top) and a healthy patient (bottom) using axial FLAIR MRI. The hydrocephalus ex vacuo in the frontal lobe isn't as impressive as that seen in the following scan (both from the same patients as in (a). The absence of lateral tissue (temporal) and the diminished shape of the frontal lobes shows overt atrophy. (b) Coronal T1-weighted MRI showing overt hydrocephalus ex vacuo of the frontal and temporal lobes, with resultant enlargement of the ventricles. The patient's left lobe (right side of image) appears to be less affected than the right lobe (left side of image). (c) High-powered light microscopy reveals Pick cells containing Pick bodies—round, intracytoplasmic inclusions. The dark circles within the purple cells are nuclei. The smaller, paler-staining structures are the Pick bodies. τ Tangles are not visible in either image.

The frontal and temporal lobes atrophy to a variable extent and with variable severity. It is asymmetrical, although the disease progression occurs comparably. The atrophic cortical regions are marked by neuronal loss and the presence of **hyperphosphorylated τ-containing** neurofibrillary tangles. Although Alzheimer's disease is characterized by the combination of Aβ and τ deposition, FTLD-τ shows only τ aggregation and accumulation. In some cases, FTLD-τ will also show smooth-contoured intracytoplasmic inclusions (Pick bodies within Pick cells). **Pick bodies** and **Pick cells** are the definitive means to differentiate **FTLD from Alzheimer's**, which you only do on autopsy. Like the other disorders of protein aggregation, there is no treatment. And for FTLD, there aren't any known medications to improve symptomology.

There is a variant of FTLD with the same disease progression and radiological findings and the same untreatable course that is not caused by τ aggregates. Several different gene mutations lead to FTLD-TDP (not spelling this out for you because we want you to learn that FTLDs are caused by τ), suggesting that there must be something about the frontal and temporal lobes that predisposes them to aggregate formation. Two different aggregates with the same outcome mean that we have identified the symptom (FTLD) and not the pathology.

Parkinson's Disease and Lewy Body Dementia

We discussed Parkinson's disease in Cortex #5: *Basal Ganglia*. It is caused by the accumulation of α-synuclein. When motor symptoms predominate, it is Parkinson's disease. The same α-synuclein aggregates also cause Lewy body dementia. When cognitive and memory impairments predominate over the parkinsonian symptoms, the disease is called Lewy body dementia. Both Parkinson's with dementia (the movement disorder predominates/develops sooner than dementia) and Lewy body dementia with parkinsonism (dementia predominates/develops sooner than the movement disorder) represent two outcomes of the same pathological process, which is caused by the aggregation of **α-synuclein** into Lewy bodies. These intracytoplasmic inclusions induce apoptosis in neurons. These aggregates have a predilection for, or at least form earliest and most severely in, the **substantia nigra** of the basal ganglia. The **loss of dopaminergic neurons** results in the inability to initiate movement. Thus, the motor symptoms are a mask-like face (diminished expression), slowed movement, cogwheel rigidity, short shuffling steps, and a pill-rolling tremor.

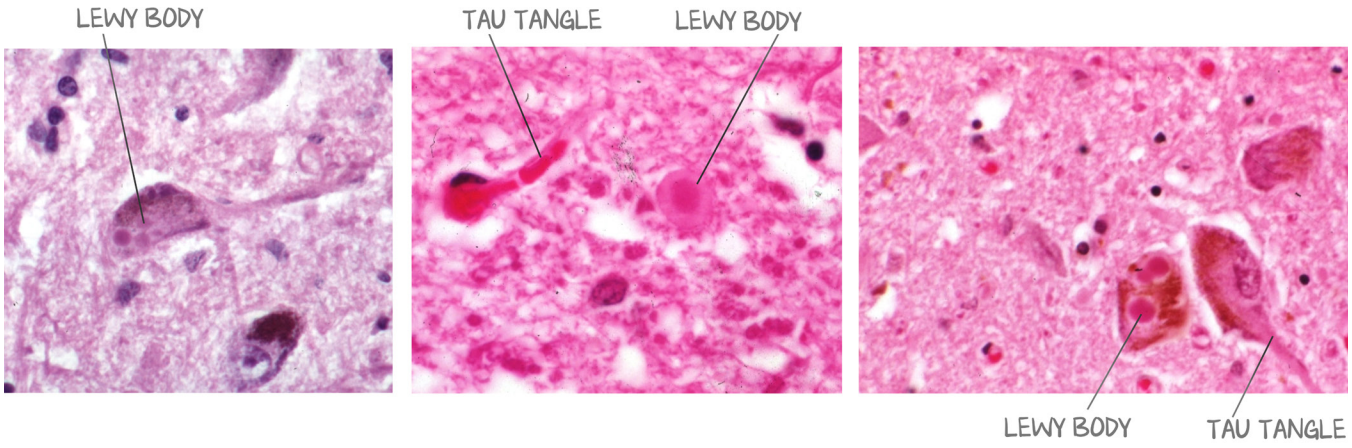

Figure 6.5: Lewy Bodies
The small, smooth, darker colored circles in each of these cells represent Lewy bodies. τ Tangles (middle image left, right image bottom right) may be present, but it is the Lewy Bodies that make this diagnosis.

Consistent with the protein aggregate theme, Lewy bodies can be released from one neuron and taken up by another, suggesting a capacity for prion-like dissemination within the brain. The progressive pattern of worsening movement disorder, worsening dementia, and eventually, symptoms of other dopaminergic pathways supports this hypothesis. α-Synuclein aggregates first appear in the medulla and then in contiguous areas of the brain, ascending through the brainstem and extending into limbic structures and, finally, the neocortex. There are links to mutations in both the **α-synuclein** gene (*SNCA*), leading to the overexpression of α-synuclein, and the parkin gene (*PRKN*), leading to mitochondrial dysfunction.

No therapy prevents the progression of neural degeneration. Parkinsonism, the movement disorder, can be treated with dopamine, as discussed in Cortex #5: *Basal Ganglia*. Although those medications treat the symptoms, they eventually stop working as the brain atrophy progresses. Unlike the other neurocognitive degeneration disorders, parkinsonism has no characteristic radiological findings, no detectable changes in the substantia nigra on MRI.

Huntington's

Huntington's disease is a neurodegenerative disorder that results in abnormal movement and, eventually, dementia. The protein **huntingtin** is encoded by the ***HTT* gene** located on **chromosome 4**. The accumulation of huntingtin aggregates can eventually claim the entire cortex, but like Parkinson's disease, the most affected area (or, more likely, the first area that demonstrates symptoms) is the basal ganglia. Whereas Parkinson's claims the substantia nigra first, Huntington's claims the **striatum**.

We left the striatum as "the striatum" in Cortex #5: *Basal Ganglia*. In truth, "the striatum" comprises the caudate nucleus, putamen, and globus pallidus. The putamen and globus pallidus together make the lentiform nucleus. All the different ways of naming nuclei or combinations of nuclei make this subject really annoying for new learners. And so, back to the cables of light we go. You are the cortex, standing on the striatum, with the globus pallidus externa (GP_{ext}) and globus pallidus interna (GP_{int}) to your left, substantia nigra off to the right, the subthalamus between you and the thalamus. A red cable runs from the substantia nigra and the GP_{int}, the default state, the thalamus silent. Green cables run from the subthalamus to the substantia nigra and GP_{int}, stimulating their inhibitory signal. The striatum has a glowing red cable to the GP_{ext} and a non-glowing black cable to the substantia nigra. Finally, a non-glowing black cable extends from the GP_{ext} to the subthalamus.

In Huntington's disease, there is **atrophy of the striatum**. This changes the default state in a big way. With the loss of the striatum, there is a loss of that glowing red cable to the left, from the striatum to the GP_{ext}. The GP_{ext} is disinhibited, and its black non-glowing cable to the subthalamus is now, by default, a glowing red cable that inhibits the subthalamus. This physiologically occurs when the cortex "dumps the bucket of dopamine" to get a movement started. The inhibition of the subthalamus turns off the glowing green cables to the GP_{int} and substantia nigra. Without that signal, the GP_{int} and substantia nigra's glowing red cables go dark. **There is no inhibition of the thalamus**. In the real disease, there isn't a total loss of the striatum, but the more striatum that is compromised, the less thalamic inhibition there will be, and so, a **disinhibited thalamus causes more movement**.

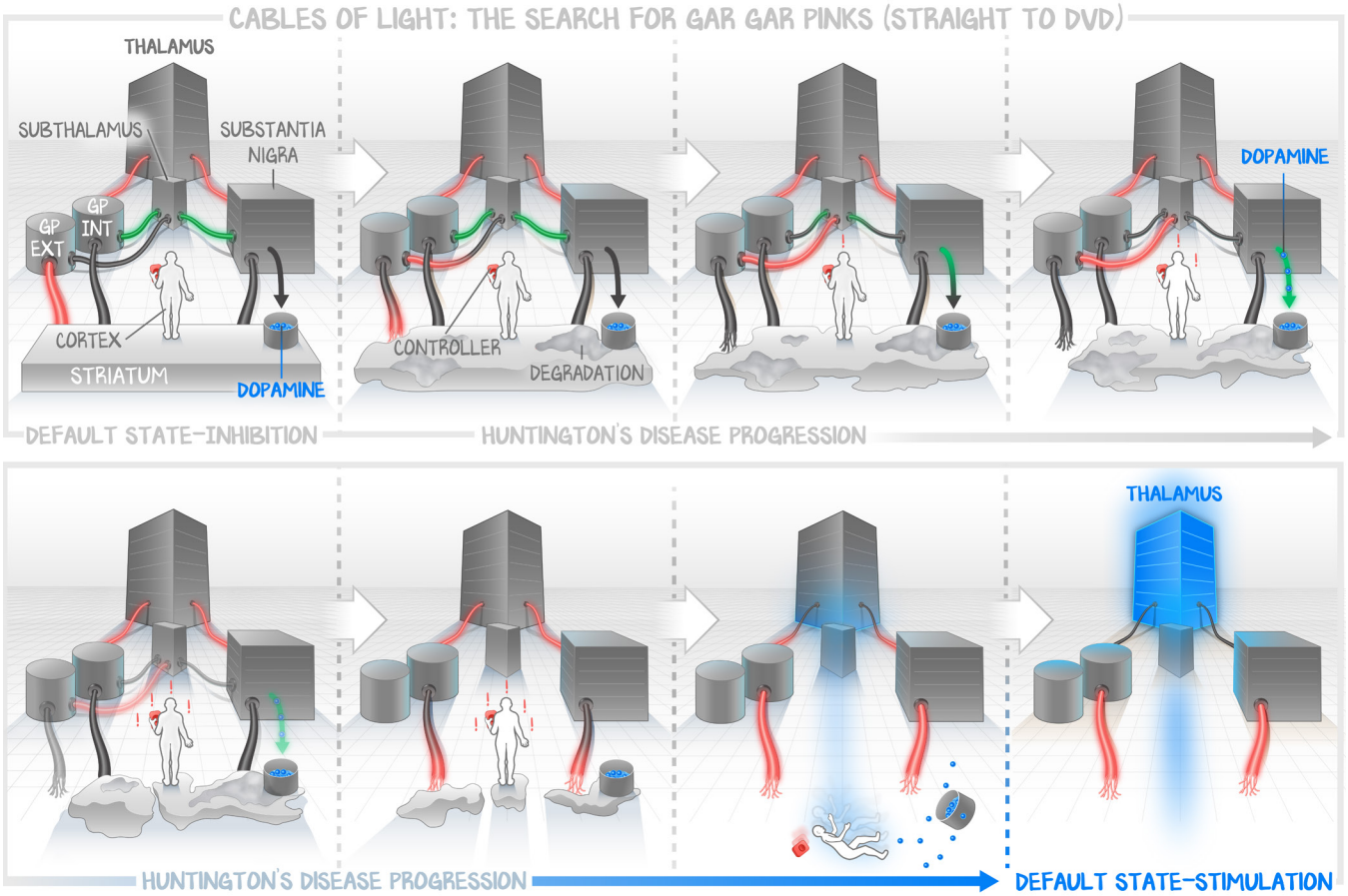

Figure 6.6: Cables of Light In Huntington's Disease
In keeping with our safely-not-a-trademark-violation theme of the basal ganglia, here is the "straight to DVD" episode, the search for Gar Gar Pinks. It doesn't get an episode because it breaks canon altogether. In Huntington's disease, the damage to the striatum (caudate nucleus) causes the indirect path to fail. No matter how hard or how many times cortex pushes on the controller (which should maintain the inhibition of movement), there is no effect. The result is the ABSENCE of INHIBITION of the globus pallidus externa, and so, the default state is always to move. The indirect pathway is lost, and so the default state of inhibition is lost.

Huntingtin aggregates are found in every area of the cortex on autopsy. The aggregates (and, therefore, the apoptosis and neuronal loss) are worst in the striatum—specifically the caudate nucleus. And like prion proteins and Parkinson's Lewy bodies, neurons demonstrate the ability to uptake the aggregates, leading to the gradual worsening of disease as more aggregates develop within neurons and become available to infect other neurons. Because this process is apoptotic, like the other disease processes discussed so far, there is no inflammation, and no inflammatory cells would be seen if a biopsy were performed. As neurons die off, both the grey matter and white matter atrophy with resultant hydrocephalus ex vacuo.

Huntington's disease is the prototypical disease that so well-characterizes **genetic anticipation**—progressive worsening of the disease burden with successive generations. The genetic defect is caused by **excess CAG trinucleotide repeats** in *HTT* exon 1. Normal *HTT* alleles have 6–35 CAG repeats. There is an inverse relationship between the repeat number and age of onset, meaning that **more repeats** tend to be associated **with earlier onset**. Repeat expansions occur during **spermatogenesis** (not gametogenesis, it seems, only spermatogenesis) such that paternal transmission is associated with early onset in the next generation as the trinucleotide repeat expands (more CAG repeats added to *HTT* in the spermatocyte from which his offspring develops). Huntington's has an **autosomal dominant**

inheritance pattern—even if one allele is normal, the presence of excess repeats on the other allele translates to bad proteins, leading to aggregates.

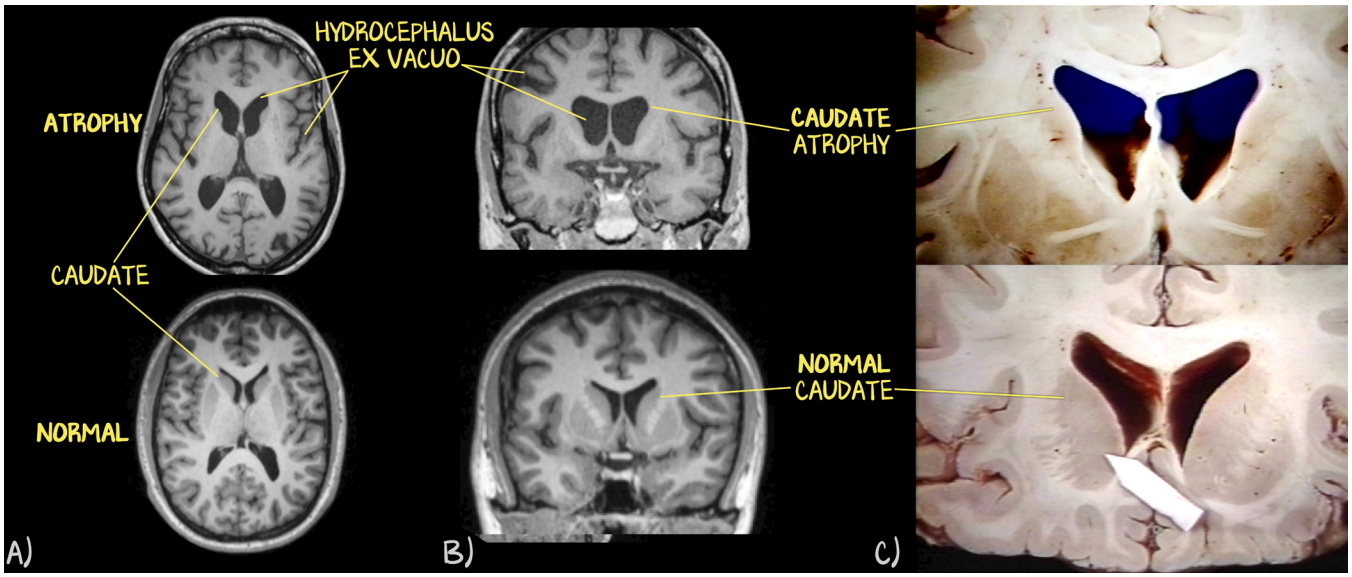

Figure 6.7: Huntington's Disease
(a) Axial T1-weighted MRI demonstrating severe atrophy of the caudate nucleus and hydrocephalus ex vacuo of the Huntington's-affected area (top) versus normal (bottom). (b) Coronal T1-weighted MRI of the same patients, again demonstrating severe atrophy of the caudate nucleus with global atrophy and hydrocephalus ex vacuo. (c) Representative gross samples with (top) and without (bottom) Huntington's showing a significant difference in caudate nucleus volume and hydrocephalus ex vacuo.

Onset is most common in the fourth and fifth decades of life but can occur at any age due to the association between symptom onset and the number of trinucleotide repeats. Motor symptoms often precede cognitive impairment. The motor dysfunction is **choreiform**, with increased and i**nvoluntary jerky movements** of all parts of the body, and **writhing** movements of the extremities are typical. There is a genetic screen, but **no treatment**. Death usually occurs due to either **infection** or **suicide**, the movement disorder and cognitive decline progressing over 10–15 years.

Citations

Figure 6.3a: Image by Patho, distributed under a CC-BY-SA-3.0 license creativecommons.org/licenses/by-sa/3.0.

Figure 6.3b: Image by KGH, distributed under a GFDL-self license creativecommons.org/licenses/by-sa/3.0.

Figures 6.3c, 6.3d, 6.3e, 6.3f, 6.4a, 6.4b, 6.7: Courtesy of Radiopaedia.

Figures 6.4c, 6.4d, 6.5: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.